

A2 in the treatment of multi-drug resistant cancers. PAN-20 and PAN-30, according to this invention, fall into this latter category.

- At page 16, starting at line 3, replace paragraph 44 with the following:

A3 [0044] Pharmaceutical compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition may be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about the including in the composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the pharmaceutical compositions may be administered in a time release formulation, for example, in a composition which includes a slow release polymer. The active compounds can be prepared with carriers that will protect the compound against rapid release, such as controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are patented or generally known to those skilled in the art.

- At page 16, starting at line 26, replace paragraph 45 with the following:

A4 [0045] Sterile injectable solutions can be prepared by incorporating an active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. Pharmaceutical compositions may be

AY formulated with one or more compounds that enhance the solubility of the active compounds.

- At page 17, replace the paragraph starting at line 5 with the following:

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Example 1: Preparation process of producing PAM-120, PBM-100, and PAN-20

- [1] Ginseng crude extract 10 g was dissolved in 40 mL of 95 % ethanol
- [2] Add 40 mL of 5 N NaOH
- [3] Pour into the reaction tank, and set temperature to 240°C, and pressure to 3.5 Mpa, for 1.5 hours
- [4] Reduce temperature to room temperature, and take the products out the tank
- [5] Add HCl to neutralize pH to about 7, and expend the volume to 800 mL using water
- [6] Extract 3 times with acetic ester, 100 mL each time
- [7] Combine all the extracts, and reduce the pressure to dry. Thus, obtain 3.8 g of dried extracts
- [8] Grind and dissolved the extract in 20 mL of methanol, and mix the methanol solution with silica gel
- [9] Dry up the mixture, and then grind to fine powder
- [10] Load the Silica gel column
- [11] Wash the column with 60 mL of ether:petroleum benzin (1:3), and thus, 250 mg of PAM-120, and 45 mg of PBM-100 were obtained
- [12] Wash the column with 90 mL of chlorofom:methanol (95:5), and thus 50 mg of PAN-20 was obtained.

- At page 17, replace the paragraph starting at line 27 with the following:

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Example 2: Another example of preparation process producing PAM-120, PBM-100, and PAN-20

- [1] 10 g of Ginseng crude extract was added into reaction tank
- [2] Add to the reaction tank 100 mL of 5 N NaOH
- [3] Set temperature to 270°C and pressure to 4.5 Mpa for 1 hour
- [4] Reduce temperature to room temperature, then take out the products
- [5] Neutralize the pH to 7 using HCl
- [6] Filter and keep the solids
- [7] Dissolve the solids in 10 mL of 95 % Ethanol
- [8] Add water to make ethanol content less than 5 %

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- [9] Sit still overnight
 - [10] Filter and keep the solids
 - [11] Dry the solids
 - [12] Dissolved the solids in 10 mL of methanol
 - [13] Filter and keep the solution
 - [14] Dry the solution to obtain 3.6 g of products
 - [15] Mix the products with 11 g of silica gel
 - [16] Grind and then load the silica gel column
 - [17] Wash the column with 100 mL of ether:petroleum benzin (1:3), and thus, 60 mg of PAM-120, and 65 mg of PBM-100 were obtained
 - [18] Wash the column with chloroform:methanol (95:5), and thus 60 mg of PAN-20 was obtained.

- At page 23, starting at line 2, replace Table 4 with the following:


Table 4. MURINE SARCOMA 180 BEARING MICE
LIFE PROLONGATION RATE

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Group	DS ₅₀	% ADS(M \pm SD)	LPR(%)
Control	14	14.7 \pm 5.4	
Rh2 (10 mg/kg)	22	24.7 \pm 12.6	68.0
PAM-120 (10 mg/kg)	38	38.6 \pm 16.4	162.6
Rh2 (25 mg/kg)	41	44.3 \pm 19.6	201.4
PAM-120 (25 mg/kg)	77	80.6 \pm 34.4	448.3

- At page 26, replace the paragraph starting at line 3 with the following:

- NA8
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 2. Lee YN, Lee HY, Chung HY, Kim SI, Lee SK, Park BC, Kim KW (1996) In vitro induction of differentiation by ginsenosides in F9 teratocarcinoma cells. Eur J Cancer. 1420-8
 3. Odashima S, Ohta T, Kohno H, Matsuda T, Kitagawa I, Abe H, Arichi S (1985) Control of phenotypic expression of cultured B16 melanoma cells by plant glycosides. Cancer Res. 85: 2781-8

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4. Xia LJ, Han R (1996) [Differentiation of B16 melanoma cells induced by ginsenoside RH2]. Yao Hsueh Hsueh Pao. 31: 742-5
 5. Kikuchi Y, Sasa H, Kita T, Hirata J, Tode T, Nagata I (1991) Inhibition of human ovarian cancer cell proliferation in vitro by ginsenoside Rh2 and adjuvant effects to cisplatin in vivo. Anti-cancer Drugs. 2: 63-7
 6. Lee KY, Park JA, Chung E, Lee YH, Kim SI, Lee SK (1996) Ginsenoside-Rh2 blocks the cell cycle of SK-HEP-1 cells at the G1/S boundary by selectively inducing the protein expression of p27kip1. Cancer Lett. 110: 193-200
 7. Oh M, Choi YH, Choi S, Chung H, Kim K, Kim SI, Kim DK, Kim ND (1999) Anti-proliferating effects of ginsenoside Rh2 on MCF-7 human breast cancer cells. Int J Oncol. 18: 869-75
 8. Ota T, Maeda M, Odashima S, Ninomiya TJ, Tatsuka M (1997) G1 phase-specific suppression of the Cdk2 activity by ginsenoside Rh2 in cultured murine cells. Life Sci. 60: PL39-44
 9. Nakata H, Kikuchi Y, Tode T, Hirata J, Kita T, Ishii K, Kudoh K, Nagata I, Shinomiya N (1998) Inhibitory effects of ginsenoside Rh2 on tumor growth in nude mice bearing human ovarian cancer cells. Jpn J Cancer Res. 89: 733-40
 10. Kim HE, Oh JH, Lee SK, Oh YJ (1999) Ginsenoside RH-2 induces apoptotic cell death in rat C6 glioma via a reactive oxygen- and caspase-dependent but Bcl-X(L)-independent pathway. Life Sci. 65: PL33-40
 11. Park JA, Lee KY, Oh YJ, Kim KW, Lee SK (1997) Activation of caspase-3 protease via a Bcl-2-insensitive pathway during the process of ginsenoside Rh2-induced apoptosis. Cancer Lett. 121: 73-81
 12. Jia W (2000) Ginsenoside Chemotherapy. U.S. Patent Provisional File – Serial No. 60/204/765
 13. Shinkai K, Akedo H, Mukai M, Imamura F, Isoai A, Kobayashi M, Kitagawa I (1996) Inhibition of in vitro tumor cell invasion by ginsenoside Rg3. Jpn J Cancer Res. 87: 357-62.
 14. Liu WK, Xu SX, Che CT (2000) Anti-proliferative effect of ginseng saponins on human prostate cancer cell line. Life Sci. 67(11):1297-306.
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 16. Mochizuki M, Yoo YC, Matsuzawa K, Sato K, Saiki I, Tono-oka S, Samukawa K, Azuma I (1995) Inhibitory effect of tumor metastasis in mice by saponins,

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ginsenoside-Rb2, 20(R)- and 20(S)-ginsenoside-Rg3, of red ginseng. Biol Pharm Bull. 18: 1197-202.

Hideo H, Jong HS, Matsumiya S, Uchiyama M, Jae DH (1999) Metabolites of Ginseng Saponins by Human Intestinal Bacteria and Its Preparation for an Anti-cancer. U.S. Patent No. 5,919,770.
